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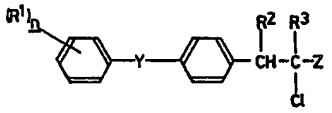
(19)

(54) 2-CHLOROPROPIONIC ACID AND ITS DERIVATIVES

(71) We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA, also known as TAKEDA CHEMICAL INDUSTRIES LIMITED, of 27, Doshomachi 2-chome, Higashi-ku, Osaka, Japan, a joint stock company of Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to 2-chloropropionic acid and its derivatives, in particular to a novel compound of the following general formula (I):



(I)

wherein R^1 represents a hydrogen atom, a lower alkyl group having 1 to 5 carbon atoms, a halogen atom, hydroxyl group, a lower alkoxy group having 1 to 4 carbon atoms or a trifluoromethyl group; R_2 and R_3 are the same or different and each represents a hydrogen atom or a lower alkyl group having 1 to 5 carbon atoms; Y represents an alkylenethio group having 1 to 6 carbon atoms, an alkyleneoxy group having 1 to 6 carbon atoms or an alkylenedioxy group having 1 to 6 carbon atoms; Z represents a carboxyl group or a group convertible to a carboxyl group; and n is 1 or 2.

We have made extensive studies on a series of 2-chloropropionic acids and their derivatives and succeeded in synthesizing the novel compound of the above formula (I), and have found that the above compounds have remarkable hypolipidemic, hypoglycemic and other biological activities.

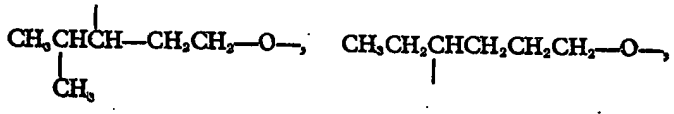
Thus, a principal object of this invention is to provide novel compounds of the formula (I) which are useful as medicines, such as remedies for hyperlipemia.

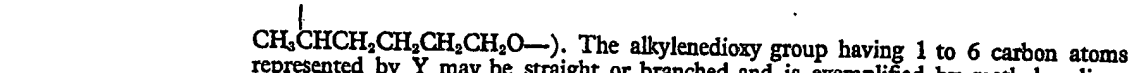
Another object of this invention is to provide methods for the production of these novel compounds.

Further objects will be made apparent from the description and claims hereinafter given.

The lower alkyl group having 1 to 5 carbon atoms represented by R^1, R^2 and R^3 may be straight or branched and are exemplified by methyl, ethyl, *n*-propyl, isopropyl *n*-butyl, isobutyl, sec.-butyl, tert.-butyl, n-pentyl, isopentyl and neopentyl. The halogen atom represented by R^1 may be chlorine, bromine, iodine or fluorine. The alkoxy group having 1 to carbon atoms represented by R^1 is exemplified by methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy and tert.-butoxy. The alkyleneoxy group

having 1 to 6 carbon atoms represented by Y may be straight or branched and is exemplified by methyleneoxy (—CH_2—O—), ethyleneoxy (—CH_2CH_2—O—, CH_3CH(—)—O—), propyleneoxy (—$CH_2CH_2CH_2$—O—, CH_3CHCH_2—O—, CH_3CH_2CH—O—, $(CH_3)_2C$—O—), butyleneoxy(—$CH_2CH_2CH_2CH_2$—O—, $CH_3CHCH_2CH_2$—O—, $CH_3CH_2CHCH_2$—O—, $CH_3CH_2CH_2CH$—O—, $(CH_3)_2CHCH$—O—, $CH_3CH_2C(CH_3)_2$—O—, $CH_3CH(CH_3)CH$—O—, —$CH_2CH_2CH(CH_3)$—O—), pentyleneoxy (e.g. $CH_3CH_2CH_2CH_2CH$—O—, $CH_3CH(CH_3)CH_2CH$—O—, $CH_3CH_2CH(CH_3)CH$—O—, $CH_3CH_2CH_2CHCH_2$—O—, $CH_3CH(CH_3)CH$—CH_2—O—, $CH_3CH_2C(CH_3)_2$—O—, $CH_3CH_2CH(CH_3)CH$—O—, $(CH_3CH_2CH_2)_2CH$—O—, $CH_3CH_2CH_2CH(CH_3)$—O—, $CH_3CH_2CHCH_2CH_2$—O—, $CH_3C(CH_3)_2CH_2$—O—, $CH_3CH(CH_3)CH_2CH_2$—O—, $CH_2CH(CH_2CH_3)CH_2$—O—, —$CH_2CH_2CH_2CH_2CH_2$—O—, $CH_3CH_2CH_2CH(CH_3)CH_2$—O—, —$CH_2CH_2CH(CH_3)CH_2$—O—, —$CH_2CH_2CH_2CH_2CH_2$—O—) and hexyleneoxy (e.g. $CH_3CH_2CH_2CH_2CH_2CH$—O—, $CH_3CHCH_2CH_2CH$—O—, $CH_3CH_2CH_2CH(CH_3)CH$—O—, $CH_3C(CH_3)_2CH_2CH$—O—, $CH_3CH_2CH_2CH_2CHCH_2$—O—, CH_3CHCH_2CH—CH_2—O—, $CH_3C(CH_3)_2CH$—CH_2—O—, $CH_3CH_2CH_2CHCH_2CH_2$—O—,





$CH_3CHCH_2CH_2CH_2CH_2O$—). The alkylenedioxy group having 1 to 6 carbon atoms represented by Y may be straight or branched and is exemplified by methylenedioxy (—O—CH_2—O—), ethylene dioxy (—O—CH_2CH_2—O—, —O—CH(CH$_3$)—O—),

propylene dioxy(—O—$CH_2CH_2CH_2O$—, —O—$CHCH_2$(CH$_3$)—O—, —O—CH(—CH_2CH_3)—O—), butylenedioxy (e.g. —O—$CH_2CH_2CH_2CH_2$—O—, —O—CH_2CH(CH$_3$)CH_2—O—

—O—CH(CH$_3$)CH(CH$_3$)—O—), pentylenedioxy (e.g. —O—$CH_2CH_2CH_2CH_2CH_2$—O—,

—O—CH(CH$_3$)$CH_2CH_2CH_2$—O—, —O—CH_2CH(CH$_3$)CH_2CH_2—O—,

—O—CH(CH$_3$)CH(CH$_3$)CH_2—O—, —O—$CHCH_2CH$(CH$_3$)—O—, —O—CH(=CH_2)CH_2CH_2—O—)

and hexylenedioxy (e.g. —O—$CH_2CH_2CH_2CH_2CH_2CH_2$—O—,

—O—CH(CH$_3$)$CH_2CH_2CH_2CH_2$—O—, —O—CH_2CH(CH$_3$)$CH_2CH_2CH_2$—O—,

—O—CH_2CH_2CH(CH$_3$)CH_2CH_2—O—, —O—CH(—CH_2CH_3)$CH_2CH_2CH_2$—O—,

—O—CH_2CH(CH$_3$)CH_2CH_2—O—, —O—$CHCH$(CH$_3$)CH_2CH_2—O—,

—O—CH_2CH(CH$_3$)$CHCH_2$—O—, —O—CH_2CH(—$CH_2CH_2CH_3$)—O—).

The alkylenethio group having 1 to 6 carbon atoms represented by Y may be straight or branched and is exemplified by methylenethio (—CH_2—S—), ethylenethio (—CH_2CH_2—S—, —CH(CH$_3$)—S—), propylenethio (—$CH_2CH_2CH_2$—S—,

CH_3CHCH_2—S—, CH_3CH_2CH(CH$_3$)—S—, CH_3C(CH$_3$)$_2$—S—),

butylenethio (—$CH_2CH_2CH_2CH_2$—S—, CH_2—$CH(CH_3)CH_2CH_2$—S—, $CH_3CH_2CH(CH_3)CH_2$—S—, $CH_3CH_2CH_2CH(CH_3)$—S—, $CH_3CH(CH_3)$—CH_2—S—, $CH_3CH_2C(CH_3)_2$—S—, $CH_3CH(CH_3)CH_2$—S—, —$CH_2CH_2CH(CH_3)$—S—),

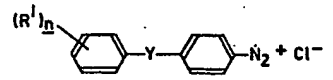
pentylenethio (e.g. $CH_3CH_2CH_2CH_2CH(CH_3)$—S—, $CH_3CH(CH_3)CH_2CH(CH_3)$—S—, $CH_3CH_2CH(CH_3)CH$—S—, $CH_3CH_2CH_2CH(CH_3)$—S—, $CH_3CH_2C(CH_3)_2CH_2$—S—, $CH_3CH_2CH(CH_3)CH(CH_3)$—S—, CH_2=$CH_2CH_2CH(CH_3)$—S—, $CH_3CH_2CH(CH_3)CH_2CH_2$—S—, $CH_3C(CH_3)_2CH_2CH_2$—S—, $CH_3CH(CH_3)CH(CH_3)CH_2$—S—, —$CH_2CH(CH_3)CH_2CH_2CH_2$—S—, $CH_3CH(CH_2CH_3)CH_2CH_2CH_2$—S—, —$CH_2CH(CH_3)CH_2CH_2CH_2$—S—, —$CH_2CH_2CH(CH_3)CH_2CH_2$—S—, —$CH_2CH_2CH_2CH_2CH_2CH_2$—S—) and hexylenethio

(e.g. $CH_3CH_2CH_2CH_2CH_2CH(CH_3)$—S—, $CH_3CH(CH_3)CH_2CH_2CH(CH_3)$—S—, $CH_3C(CH_3)_2CH_2CH(CH_3)$—S—, $CH_3CH_2CH_2CH_2CH(CH_3)CH_2$—S—, $CH_3CH(CH_3)CH_2CH(CH_3)CH_2$—S—, $CH_3CH_2CH_2CH(CH_3)CH_2CH_2$—S—, $CH_3CH_2CH(CH_3)CH(CH_3)CH_2$—S—, $CH_3CH_2CH_2CH_2CH_2CH_2CH_2$—S—, $CH_3CH(CH_3)CH_2CH_2CH_2CH_2$—S—).

As the group convertible to a carboxyl group, represented by Z the following are examples: formyl group, cyano group, aminocarbonyl group, an alkoxycarbonyl group having 2 to 5 carbon atoms (e.g. methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, *i*-propoxycarbonyl, *n*-butoxycarbonyl, isobutoxycarbonyl, tert.-butoxycarbonyl, sec.-butoxycarbonyl), a mono- or di-alkylaminocarbonyl group having 2 to 9 carbon atoms (e.g. N-methylaminocarbonyl, N,N-dimethylaminocarbonyl, N-ethylaminocarbonyl, N,N-diethylaminocarbonyl, N-*n*-propylaminocarbonyl, N,N-di-*n*-propylaminocarbonyl, N - isopropylaminocarbonyl, N,N - diisopropylaminocarbonyl, N - *n* - butylaminocarbonyl, N,N-di-*n*-butylaminocarbonyl), mono- or di-cycloalkylaminocarbonyl having 6 to 13 carbon atoms (e.g. N-cyclopentylaminocarbonyl, N,N-dicyclopentylaminocarbonyl, N-cyclohexylaminocarbonyl, N,N-dicyclohexylaminocarbonyl), mono- or diarylaminocarbonyl having 7 to 16 carbon atoms (e.g. N-phenylaminocarbonyl, N,N-diphenylaminocarbonyl, N-tolylaminocarbonyl, N,N-ditolylaminocarbonyl). The compound (I) wherein Z is a carboxyl group includes pharmaceutically acceptable salts thereof. The pharmaceutically acceptable salts are exemplified by a salt of the carboxylic acid with nontoxic cations (e.g. sodium, potassium, lithium, calcium, magnesium or ammonium) or with organic amines such as polyhydroxyalkylamines (e.g. N-methylglucamine, diethanolamine, triethanolamine or trishydroxymethylaminomethane).

The compounds of the general formula (I) have prominent hypolipidemic and hypoglycemic activity and show low toxicity and low side effects. Taking advantage of these properties these compounds can safely be used as remedies for hyperlipemia and diabetes in mammals, including human beings. When a compound (I) is used as such as a medicine, it can be administered, either as such or in admixture with a pharmaceutically acceptable vehicle, excipient and/or diluent, orally or parenterally in various dosage forms such as powders, granules, tablets, capsules, suppositories and injections. When any of the compounds is used for the purpose of treating hyperlipemia, it may be administered orally or non-orally in amounts of 0.03—1.0 g. per day for a human adult. When any of the compounds is used for the purpose of treating diabetes, it may be administered orally or non-orally in amounts of 0.1—3.0 g. per day for a human adult.

The compounds of formula (I) can be prepared by reacting a diazonium salt of formula (II):



(II)

wherein R^1, Y and *n* have the same meanings as given above, with an ethylene compound of the general formula (III):

$$R^2CH=CR^3—Z \qquad \text{(III)}$$

wherein R^2, R^3 and Z have the same meanings as given above.

This reaction is advantageously conducted with a slight molecular excess of the ethylene compound (III) relative to the diazonium salt (II). The reaction is usually carried out in a solvent. The solvent is exemplified by water, methanol, ethanol, *n*-propanol, acetone, methyl ethyl ketone, diethyl ketone, ethyl propyl ketone, acetonitrile, N-methylpyrrolidone, dimethylsulfoxide or sulfolane, as well as mixtures of such solvents. The reaction is preferably conducted by adding hydrochloric acid to the reaction system. When a solvent containing hydrochloric acid is used, diazonium salts (II) containing an anion other than a chlorine atom can be employed as a starting material in this invention. Moreover, the reaction may be accelerated with advantage by using a catalyst. As the catalyst, copper compounds, for instance, may be employed. Thus, cuprous oxide, cupric oxide, cuprous chloride, cupric chloride, cuprous bromide, cupric bromide, copper nitrate or copper sulphate are more commonly employed. Among them, cuprous oxide is the most preferred. The proportion of the catalyst is generally 0.02 to 0.2, preferably 0.05 to 0.1, mole per mole of the diazonium salt (II). To control the reaction velocity, the above-mentioned catalyst may be used in an increased or in a reduced amount. The temperature, time, pressure and other conditions of the reaction are selected according to the particular starting materials, solvent and catalyst and so on. Ordinarily the reaction proceeds smoothly at a temperature under cooling with ice to room temperature.

When Z in the compound thus obtained is a carboxyl group, it may be converted by a known manner to a pharmaceutically acceptable salt of the carboxyl group with a

nontoxic cation or with an organic amine which are mentioned hereinbefore or to an ester such as a methyl ester, ethyl ester, *n*-propyl ester or isopropyl ester. When Z in compound (I) is a group convertible to a carboxyl group, the group may be converted to the carboxyl group in a known manner. When Z is a cyano group, an alkoxycarbonyl group or an aminocarbonyl group which is substituted or unsubstituted, it can be converted to a carboxyl group by means of hydrolysis, whereas when Z is a formyl group, it can be oxidized to a carboxyl group. When Z is a cyano group, it can also be converted to an amino carbonyl group. For instance, the hydrolysis may be effected by treating the compound (I) with an acid such as hydrochloric acid, sulphuric acid, nitric acid, phosphoric acid or carbonic acid or with a base such as sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate. In this reaction, an alcohol such as methanol or ethanol may be present as required. The oxidation of the formyl group can be accomplished by permitting an oxidising agent to act upon the compound (I) in a suitable solvent. Examples of suitable oxidizing agents include potassium dichromate, potassium chromate, potassium permanganate, hydrogen peroxide barium peroxide, peracetic acid, perbenzoic acid, hypochlorous acid and ozone. The temperature, time and other conditions of the above-mentioned hydrolysis and oxidation reaction are selected according to factors such as the desired compound (I), solvent and procedure followed.

The compound (I) thus obtained may be separated and purified by known separation and purification procedures such as crystallization, recrystallization, concentration, distillation or chromatography.

The starting material diazonium salt (II) can be prepared by diazotizing the corresponding amino compound in the presence of a hydrochloric acid in a conventional manner or by bringing a diazonium salt (II) containing an anion other than chlorine into contact with hydrochloric acid.

Throughout the present specification, the abbreviations "mg.", "g.", "ml", "m.p.", "b.p." and "°C", respectively refer to "milligram(s)", "gram(s)", "millilitre(s)", "melting point", "boiling point" and "degree(s) centigrade".

Reference Example 1.

31.2 g. of phenol are dissolved in 120 ml. of ethanol and 24 g. of a methanol solution containing 28% of sodium methoxide and 0.3 g. of potassium iodide are added. Then 20 g. of 4-(2-bromoethyl)acetanilide are added to the mixture, and the mixture is refluxed for 3.5 hours. After the solvent is distilled off, an aqueous solution of sodium hydroxide in 200 ml. of water is added to the residue, and the crystals formed are collected by filtration. Recrystallization from ethyl acetate gives 12 g. of 4-(2-phenoxyethyl)acetanilide, melting at 121—123° C.

10 g. of 4-(2-phenoxyethyl)acetanilide are added to a mixed solution of 30 ml. of hydrochloric acid and 20 ml. of water and the mixture is refluxed for 2 hours. After cooling, the crystals formed are collected by filtration. Recrystallization from water gives 7.5 g. of 4-(2-phenoxyethyl)aniline hydrochloride, melting at 189—191° C.

Reference Example 2.

A mixture of 37.8 g. of 1-phenyl-1-bromo-2-methylpropane, 23.6 g. of *p*-nitrophenol, 150 ml. of ethanol and 9.5 g. of sodium methoxide is refluxed for 5 hours. After the reaction has been completed, ethanol is distilled off and the residue is extracted with ether. The extract is washed with a 5% aqueous solution of sodium hydroxide and then with water. After drying with magnesium sulphate, the solvent is distilled off. The resulting red oily substance which is crude 1-phenyl-1-(4-nitrophenoxy)-2-methylpropane is dissolved in 100 ml. of methanol, and subjected to catalytic reduction using palladium-carbon. After the reduction has been completed, the catalyst is removed by filtration. The oily substance obtained by removing the solvent is dissolved in 50 ml. of ether, and concentrated hydrochloric acid is added to the solution to give 4-(1-phenyl-2-methylpropyloxy)aniline hydrochloride, melting at 165—168° C.

Reference Example 3.

A mixture of 240 g. of *p*-chlorobenzyl chloride, 240 g. of *p*-acetamidophenol, 850 ml. of ethanol and 290 g. of a 28% methanolic solution of sodium methoxide is stirred under heating over a mantle heater. The reaction begins suddenly in the neighborhood of 65° C. and the mixture starts to reflux vigorously. (The mantle heater is removed.) The reaction mixture is refluxed for 2.5 hours, after which about 700 ml. of the solvent are distilled off. The residue is poured into one litre of a 4% aqueous solution of NaOH (containing ice) and the resultant precipitate of 4-acetamidophenoxy-4-chlorophenylmethane (white crystals) is collected by filtration.

The white crystals obtained in the above procedure are not dried but are directly dissolved in 1.5 kg. of *n*-propanol and, after the addition of 120 g of NaOH granules, the solution is refluxed with stirring for 5 hours. After the reaction has been completed, the mixture is concentrated under reduced pressure to remove about 600 ml. of the solvent and, with stirring, 2 kg. of ice-water is added. The resultant precipitate of 4-(4-chlorobenzyloxy)aniline (brown granules) is collected by filtration and washed with water. Yield 324 g. Melting Point: 102° C.

Reference Example 4.

25 g. of 4-(4-chlorophenoxymethyl)nitrobenzene are dissolved in 500 ml. of methanol and, with the addition of Raney nickel, the solution is shaken in a hydrogen stream. A total of 2.5 l. of hydrogen is absorbed. The Raney nickel is filtered off and the filtrate is concentrated to about 40 ml. The resultant crystals are collected by filtration. The procedure yields 3.5 g. of 4-(4-chlorophenoxymethyl)-aniline, melting at 125—126° C.

Example 1—(1)

94 g. of 4-(4-chlorobenzyloxy)aniline are dissolved in 500 ml. of acetone and, at room temperature, a mixture of 200 g. of hydrochloric acid and 100 g. of water is added. The solution is cooled well with ice. While the solution is stirred, a solution of 30.8 g. of sodium nitrite in 100 ml. of water, then 100 g. of ethyl acrylate and, finally, 5.8 g. of powdery cuprous oxide are added. Nitrogen gas is evolved in small amounts. The ice bath is removed after 10 minutes and, at 12° C., 5.8 g. of cuprous oxide are further added. With the evolution of nitrogen gas at a moderate rate, the temperature increases gradually. The mixture is stirred at room temperature for 7 hours. After the reaction has been completed, the reaction mixture is concentrated under reduced pressure and extracted with ethyl acetate. The ethyl acetate is distilled off and the residual red-colored oil is purified by chromatography on silica gel. The described procedure yields 70 g. of ethyl 2-chloro-3-[4-(4-chlorobenzoyloxy)phenyl]propionate as a yellowish oily product. Cyclohexane/benzene is used as the eluant solvent (First 1:1 and then 1:4).

NMR spectrum (δ ppm, CCl_4):

1.17 (3H, t), 3.01—3.21(2H, m), 4.08(2H, q), 4.23(1H, t), 4.89(2H, s), 6.74(2H, d), 7.02(2H, d), 7.22(4H, s)

Examples 1—(2)—1—(37).

By a similar manner to Example 1—(1), the following compounds are produced.

Example	Produced-compound	Starting compounds
1–(2)	2-chloro-3-[4-(4-chlorobenzyloxy)-phenyl]propionic acid m.p. 119–121°C	4-(4-chlorobenzyloxy)aniline, acrylic acid
1–(3)	ethyl 2-chloro-3-[4-(2-chlorobenzyl-oxy)phenyl]propionate yellow oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.16(3H,t), 3.07–3.26 (2H,m), 4.13(2H,q), 4.38 (1H,t), 5.07(2H,s), 6.79–7.60(8H,m)	4-(2-chlorobenzyloxy)aniline, ethyl acrylate
1–(4)	ethyl 2-chloro-3-[4-(4-methyl-benzyloxy)phenyl]propionate m.p. 20–24°C NMR spectrum (δ ppm, $CDCl_3$) 1.22(3H,t), 2.37(3H,s), 3.23(2H,m), 4.20(2H,q), 4.40(1H,t), 5.02(2H,s), 6.74–7.54(8H,m)	4-(4-methylbenzyloxy)aniline, ethyl acrylate
1–(5)	ethyl 2-chloro-3-[4-(4-methoxy-benzyloxy)phenyl]propionate NMR spectrum (δ ppm, $CDCl_3$) 1.13(3H,t), 3.15(2H,m), 3.68(3H,s), 4.10(2H,q), 4.35(1H,t), 4.86(2H,s), 6.7–7.5(8H,m)	4-(4-methoxybenzyloxy)aniline, ethyl acrylate
1–(6)	ethyl 2-chloro-3-(4-benzyloxy-phenyl)propionate yellow oily substance NMR spectrum (δ ppm, CCl_4) 1.12(3H,t), 3.00–3.22(2H,m), 4.06(2H,q), 4.25(1H,t), 4.90(2H,s), 6.80(2H,d), 7.01(2H,d), 7.27(5H,s)	4-benzyloxyaniline, ethyl acrylate
1–(7)	methyl 2-chloro-2-methyl-3-[4-(2-fluorobenzyloxy)phenyl]propionate yellow oil NMR spectrum (δ ppm, $CDCl_3$) 1.6(3H,s), 3.3(2H,s), 3.7(3H,s), 5.1(2H,s), 7.2(8H,m)	4-(2-fluorobenzyloxy)aniline, methylmethacrylate
1–(8)	ethyl 2-chloro-3-[4-(2-phenyl-ethyloxy)phenyl]propionate yellow oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.2(3H,t), 3.2(4H,m), 4.2(5H,m), 6.8(2H,d), 7.1(2H,d), 7.25(5H,s)	4-(2-phenylethyloxy)aniline, ethyl acrylate

Example	Produced-compound	Starting compounds
1–(9)	methyl 2-chloro-3-[4-(2-phenylethyloxy)phenyl]propionate red oily substance IR spectrum (cm^{-1}) 1740, 1605, 1505, 1240, 1015, 750, 700	4-(2-phenylethyloxy)aniline, methyl acrylate
1–(10)	ethyl 2-chloro-3-{4-[2-(4-chlorophenoxy)ethoxy]phenyl}propionate needles m.p. 81–82°C	4-[2-(4-chlorophenoxy)ethyloxyaniline, ethyl acrylate
1–(11)	ethyl 2-chloro-3-[4-(4-chlorophenoxymethyl)phenyl]propionate NMR spectrum (δ ppm, $CDCl_3$) 1.20(3H,t), 3.22(2H,m), 4.07(2H,q), 4.43(1H,t), 4.97(2H,s), 6.7–7.5 (8H,m)	4-(4-chlorophenoxymethyl)aniline, ethyl acrylate
1–(12)	2-chloro-3-(4-benzyloxyphenyl)-propionamide m.p. 134–135°C	4-benzyloxyaniline acrylamide
1–(13)	2-chloro-3-[4-(2-phenylethyloxy)-phenyl]propionamide m.p. 101°C	4-(2-phenylethyloxy)aniline acrylamide
1–(14)	ethyl 2-chloro-3-[4-(3-phenylpropyloxy)phenyl]propionate oily substance NMR spectrum (δ ppm, $COCl_3$) 1.20(3H,t), 2.09(2H,m), 2.80(2H,t), 3.20(2H,m), 3.93(2H,t), 4.18(2H,q), 4.39(1H,t), 6.80(2H,d), 7.10(2H,d), 7.20(5H,s)	4-(3-phenylpropyloxy)aniline ethyl acrylate
1–(15)	ethyl 2-chloro-3-[4-(4-phenylbutyloxy)phenyl]propionate yellow oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.17(3H,t), 1.73(4H,m), 2.63(2H,t), 3.15(2H,m), 3.87(2H,t), 4.10(2H,q), 4.33(1H,t), 6.7–7.4(9H,m)	4-(4-phenylbutyloxy)aniline, ethyl acrylate
1–(16)	ethyl 2-chloro-3-(4-benzylthiophenyl)propionate oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.20(3H,t), 3.20(2H, m), 4.09(2H,s), 4.18(2H,q), 4.40(1H,t), 6.90–7.60 (9H,m)	4-benzylthioaniline hydrochloride ethyl acrylate

Example	Produced-compound	Starting compounds
1–(17)	ethyl 2-chloro-3-[4-(4-fluoro-benzyloxy)phenyl]propionate NMR spectrum (δ ppm, $CDCl_3$) 1.09(3H,t), 3.15(2H,m), 4.06(2H,q), 4.35(1H,t), 4.83(2H,s), 6.7–7.5 (8H,m)	4-(4-fluorobenzyloxy)aniline, ethyl acrylate
1–(18)	ethyl 2-chloro-3-[4-(3-fluoro-benzyloxy)phenyl]propionate oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.17(3H,t), 3.19(2H,m), 4.13(2H,q), 4.36(1H,t), 4.97(2H,s), 6.67–7.53 (8H,m)	4-(3-fluorobenzyloxy)aniline hydrochloride ethyl acrylate
1–(19)	ethyl 2-chloro-3-[4-(2-fluoro-benzyloxy)phenyl]propionate yellow oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.19(3H,t), 2.87–3.53(2H,m), 4.16(2H,q), 4.39(1H,t), 5.08(2H,s), 6.82–7.62(8H,m)	4-(2-fluorobenzyloxy)aniline, ethyl acrylate
1–(20)	2-chloro-3-[4-(3-chlorobenzyloxy)-phenyl]propionic acid m.p. 88–89°C	4-(3-chlorobenzyloxy)aniline acrylic acid
1–(21)	ethyl 2-chloro-3-[4-(3-trifluoro-methylbenzyloxy)phenyl]propionate oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.20(3H,t), 3.20(2H,m), 3.80–4.60 (3H,m), 5.05(2H,s), 6.70–7.90(8H,m)	4-(3-trifluoromethylbenzyloxy)-aniline, ethyl acrylate
1–(22)	N-phenyl-2-chloro-3-[4-(4-chloro-benzyloxy)phenyl]propionamide white crystal m.p. 177–178°C	4-(4-chlorobenzyloxy)aniline, N-phenylacrylamide
1–(23)	N-isopropyl-2-chloro-3-[4-(2-phenyl-ethyloxy)phenyl]propionamide white crystal m.p. 98–99°C	4-(2-phenylethyloxy)aniline, N-isopropylacrylamide
1–(24)	N-methyl-N-(n-butyl)-2-chloro-3-[4-(2-phenylethyloxy)phenyl]-propionamide oily substance NMR spectrum (δ ppm, CCl_4) 0.91(3H,t), 1.33(4H,br), 2.84(3H,d), 3.09(2H,t), 3.27(2H,t), 2.80–3.63 (2H,m), 4.08(2H,t), 4.33–4.56(1H,m), 6.73(2H,d), 7.07(2H,d), 7.16(5H,s)	4-(2-phenylethyloxy)aniline N-methyl-N-(n-butyl)acrylamide

Example	Produced-compound	Starting compounds
1–(25)	ethyl 2-chloro-3-(4-phenoxymethylphenyl)propionate NMR spectrum (δ ppm, $CDCl_3$) 1.17(3H,t), 3.21(2H,m), 4.11(2H,q), 4.40(1H,t), 4.97(2H,s), 6.7–7.5 (5H,m)	4-phenoxymethylaniline ethyl acrylate
1–(26)	ethyl 2-chloro-3-[4-(1-phenylethyloxy)phenyl]propionate yellow oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.10(3H,t), 1.58(3H,d), 2.79–3.43 (2H,m), 4.07(2H,q), 4.30(1H,t), 5.23(1H,q), 6.77(2H,d), 6.96(2H,d), 7.23(5H,s)	4-(1-phenylethyloxy)aniline ethyl acrylate
1–(27)	ethyl 2-chloro-3-[4-(2-phenoxyethyloxy)phenyl]propionate m.p. 80–81°C	4-(2-phenoxyethyloxy)aniline ethyl acrylate
1–(28)	ethyl 2-chloro-3-[4-(1-phenylpropyloxy)phenyl]propionate yellow oily substance NMR spectrum (δ ppm, $CDCl_3$) 0.93(3H,t), 1.09(3H,t), 1.83(2H,q), 2.77–3.49(2H,m), 4.07(2H,q), 4.29(1H,t), 4.95(1H,t), 6.76(2H,d), 6.97(2H,d), 7.23(5H,s)	4-(1-phenylpropyloxy)aniline ethyl acrylate
1–(29)	ethyl 2-chloro-3-[4-(1-phenylbutyloxy)phenyl]propionate yellow oily substance NMR spectrum (δ ppm, $CDCl_3$) 0.77–2.13(7H,m), 1.13(3H,t), 2.78–3.43(2H,m), 4.08(2H,q), 4.33(1H,t), 5.05(1H,t), 6.76(2H,d), 6.96(2H,d), 7.26(5H,s)	4-(1-phenylbutyloxy)aniline ethyl acrylate
1–(30)	ethyl 2-chloro-3-[4-(1-phenyl-2-methylpropyloxy)phenyl]propionate yellow oily substance NMR spectrum (δ ppm, $CDCl_3$) 0.85–1.29(9H,m), 1.87–2.43(1H,m), 2.79–3.47(2H,m), 4.11(2H,q), 4.33(1H,t), 4.77(1H,d), 6.76(2H,d), 7.00(2H,d), 7.27(5H,s)	4-(1-phenyl-2-methylpropyloxy)-aniline ethyl acrylate
1–(31)	ethyl 2-chloro-3-[4-(1-phenylpentyloxy)phenyl]propionate oily substance NMR spectrum (δ ppm, $CDCl_3$) 0.67–2.30(12H,m), 3.10(2H,m), 4.17(2H,m), 4.37(1H,t), 5.08(1H,t), 6.90(4H,q), 7.30(5H,s)	4-(1-phenylpentyloxy)aniline ethyl acrylate

Example	Produced-compound	Starting compounds
1–(32)	ethyl 2-chloro-3-[4-(1-phenoxy-ethyl)phenyl]propionate NMR spectrum (δ ppm, $CDCl_3$) 1.12(3H,t), 1.56(3H,d), 3.16(2H,m), 4.08(2H,q), 4.38(1H,t), 5.21(1H,q), 6.6–7.4(9H,m)	4-(1-phenoxyethyl)aniline ethyl acrylate
1–(33)	ethyl 2-chloro-3-[4-(1-methyl-2-phenylethyloxy)phenyl]propionate oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.17(3H,t), 1.20(3H,d), 2.90(4H,m), 4.13(2H,q), 4.33(1H,t), 4,46(1H,m), 6.77(2H,d), 7.07(2H,d), 7.17(5H,s)	4-(1-methyl-2-phenylethyloxy)-aniline ethyl acrylate
1–(34)	2-chloro-3-[4-(1-phenylethyloxy)-phenyl]propionamide brown oily substance NMR spectrum (δ ppm, $CDCl_3$) 1.59(3H,d), 2.80–3.50(2H,m), 4.26–4.47(1H,m), 5.26(1H,q), 6.43(2H,br), 6.80(2H,d), 7.04(2H,d), 7.31(5H,s)	4-(1-phenylethyloxy)aniline acrylamide
1–(35)	N-phenyl-2-chloro-3-[4-(1-phenyl-ethyloxy)phenyl]propionamide m.p. 90–91°C	4-(1-phenylethyloxy)aniline N-phenyl acrylamide
1–(36)	2-chloro-3-[4-(1-phenylethyloxy)-phenyl]propionic acid colorless oily substance NMR spectrum (δ ppm, CCl_4) 1.57(3H,d), 3.10(2H,m), 4.27(1H,t), 5.17(1H,q), 6.70(2H,d), 6.97(2H,d), 7.20(5H,s), 11.53(1H,s)	4-(1-phenylethyloxy)aniline acrylic acid
1–(37)	2-chloro-3-[4-(1-phenylpropyloxy)-phenyl]propionic acid yellow oily substance NMR spectrum (δ ppm, $CDCl_3$) 0.97(3H,t), 1.90(2H,m), 3.10(2H,m), 4.33(1H,t), 4.97(1H,t), 6.73(2H,d), 7.03(2H,d), 7.23(5H,s), 8.67(1H,s)	4-(1-phenylpropyloxy)aniline acrylic acid

Example 2—(1).

5.0 g. of ethyl 2-chloro-3-[4-(4-chlorobenzyloxy)phenyl)propionate are dissolved in 40 ml. of methanol and 6.0 g. of a 20% aqueous solution of sodium hydroxide are added. The mixture is stirred at room temperature for 3 hours and the resultant white crystals are collected by filtration and washed with ether. The procedure yields 3.9 g. of sodium 2-chloro-3-[4-(4-chlorobenzyloxy)phenyl]propionate, monohydrate as white crystals melting at 218—221° C.

Examples 2—(2)—2—(4).

By a similar manner to Example 2—(1), the following salts are produced from the corresponding esters.

Example	Product Salt
2—(2)	sodium 2-chloro-3-(4-benzyloxyphenyl)-propionate-monohydrate m.p. 214—216°C
2—(3)	sodium 2-chloro-3-[4-(1-phenylethyloxy)-phenyl]propionate-monohydrate m.p. 171—174°C
2—(4)	sodium 2-chloro-3-[4-(1-phenylpropyloxy)-phenyl]propionate m.p. 183—184°C

Example 3.

7.5 g. of 4-(2-phenoxyethyl)aniline hydrochloride are dissolved in 60 ml. of acetone, followed by the addition of 7.5 ml. of hydrochloric acid, the mixture being kept at not higher than 10° C. Under stirring, a solution of 2.3 g. sodium nitrite in 4.5 ml. water is added, and the mixture is kept at the same temperature for 30 minutes. 25 ml. of ethyl acrylate are added to the mixture and, under stirring cuprous oxide is added in small portions until evolution of gas has ceased. The mixture is extracted with ether and the extract is washed three times with water, after which the solvent is distilled off. The residue is dissolved in 70 ml. of ethanol, and, under stirring and ice cooling, a solution of 1.2 g. of sodium hydroxide in 4 ml. water is added. After one hour, the resultant crystals are collected by filtration and dried. Recrystallization from ligroine gives 4.5 g. of 2-chloro-3-[4-(2-phenoxyethyl)phenyl]propionic acid. Melting point: 97—99° C.

Example 4.

6.6 g. of ethyl 2-chloro-3-[4-(1-phenylethyloxy)phenyl]propionate are dissolved in 40 ml. of methanol and, under cooling with ice and stirring, a solution of 0.8 g. sodium hydroxide in 1.2 ml. water is added. The mixture is kept under the same conditions for 3 hours, after which the solution is neutralized with acetic acid. Then the solution is concentrated to dryness. The residue is washed well with cyclohexane and dissolved in water. After treating with activated carbon, the solution is acidified with hydrochloric acid. The resultant oily substance is extracted with chloroform and the chloroform is distilled off to give 4 g. of 2-chloro-3-[4-(1-phenylethyloxy)phenyl]-propionic acid as a colourless oily substance.

NMR spectrum (δ ppm CCl_4)
1.57(3H, d), 3.10(2H, m), 4.27(1H, t), 5.17(1H, q),
6.70(2H, d), 6.97(2H, d), 7.20(5H, s), 11.53(1H, s).

Example 5—(1).

1.46 g of 2-chloro-3-[4-(4-chlorobenzyloxy)phenyl]propionic acid are dissolved in 40 ml. of ethanol followed by the addition of 0.25 g. of potassium hydroxide. The mixture is stirred at room temperature for 1 hour and the resultant crystals are collected by filtration. These crystals are recrystallized from water to obtain 1.2 g. of potassium 2-chloro-3-[4-(4-chlorobenzyloxy)phenyl]propionate, melting point: 161—162° C.

Example 5—(2).
By a similar manner to Example 5—(1), the following salt is obtained.

Example	Produced-compound
5—(2)	potassium 2-chloro-3-[4-(1-phenylethyloxy)-phenyl]propionate m.p. 148—150°C

Example 6.

5.3 g. of 4-(3-phenoxypropyl)aniline hydrochloride are dissolved in 40 ml. of acetone, followed by the addition of 5 ml. of hydrochloric acid, and the mixture is kept at not higher than 10° C. Under stirring, a solution of 1:52 g. of sodium nitrite in 3 ml. water is added and the mixture is kept at the same temperature for 30 minutes. 16 ml. of acrylic acid are added to the mixture, and under stirring at 0—5° C., cuprous oxide is added in small portions until evolution of gas has ceased. The reaction mixture is concentrated to dryness under reduced pressure. Dilute hydrochloric acid is added to the mixture and the mixture is extracted with benzene. The benzene layer is washed with water and an aqueous solution of 2 g. anhydrous sodium carbonate in 100 m. water is added. The resultant crystals are heated to dissolve them and then cooled. The crystals formed are collected by filtration and washed with a small volume of water and ethanol and dried under reduced pressure. The described procedure gives 4 g. of sodium 2-chloro-3-[4-(3-phenoxypropyl)phenyl]propionate. Melting point: 195—196° C.

Example 7.

70 g. of 4-(3-chlorobenzyloxy)aniline are dissolved in 600 ml. of acetone followed by the addition of 100 ml. of hydrochloric acid. Under stirring and cooling with ice, a solution of 22.8 g. sodium nitrite in a sufficient volume of water to make 45 ml. is slowly added. The mixture is stirred under the same conditions for 30 minutes, after which 250 ml. of ethyl acrylate are added. While this reaction mixture is maintained at 24—26° C., cuprous oxide is added in small portions until the evolution of gas has ceased. Then, 200 ml. of ether are added and the organic layer is washed three times with water. The solvent is thoroughly distilled off and the residue is dissolved in 900 ml. of ethanol. Under cooling with ice and stirring, a solution of 15 g. sodium hydroxide in a sufficient water to make 40 ml. is slowly added. Thereafter, the mixture is stirred under the same conditions for 1.5 hours and the resulting crystals are collected by filtration. Recrystallization from dilute ethanol yields 55 g. of sodium 2-chloro-3-[4-(3-chlorobenzyloxy)phenyl]propionate, melting point: 205—208° C.

Example 8.

300 mg. of sodium 2-chloro-3-[4-(1-phenylpropyloxy)phenyl]propionate are dissolved in 10 ml. of water, followed by the addition of an excess volume of an aqueous solution of calcium chloride. The oily substance separated out is extracted with a mixture of ether and ethyl acetate (1:1). The extract is washed with water and the precipitate formed is filtered off. The solvent is distilled off and the residue is subjected to recrystallization from 4 ml. of 50% aqueous ethanol. The described procedure gives 150 mg. of calcium 2-chloro-3-[4-(1-phenylpropyloxy)phenyl]propionate. Melting point: 145° C.

Example 9—(1).

1.0 g. of 2-chloro-3-[4-(1-phenylethyloxy)phenyl]propionic acid are dissolved in 20 ml. of tetrahydrofuran. Under cooling and stirring, 0.33 g. of triethylamine and then 0.34 g. of ethyl chlorocarbonate are added dropwise. The resultant white precipitates are filtered off. 0.31 g. of aniline are added dropwise to the filtrate under cooling with ice and stirring. The mixture is stirred for about 2 hours. After the tetrahydrofuran is distilled off, chloroform is added. The chloroform layer is washed with dilute hydrochloric acid and dried over magnesium sulphate. After the chloroform is distilled off, the resultant oil is purified by column chromatography, to give 580 mg. of an oil. A mixture of petroleum ether and methanol is added to this oil,

and the resultant crystals are collected by filtration. Recrystallization from petroleum ether gives N-phenyl-2-chloro-3-[4-(1-phenylethyloxy)phenyl]propionamide.
Melting point: 90—91° C.

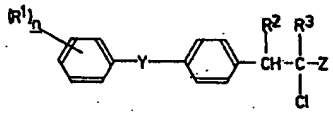
Examples 9—(2)—9—(3).

By a similar manner to Example 9—(1), the following compounds are produced.

Example	Produced-compound
9—(2)	N-butyl-2-chloro-3-[4-(1-phenylethyloxy)-phenyl]propionamide oily substance NMR spectrum (δ ppm $CDCl_3$) 0.78(3H,t), 1.0—1.6(4H,m), 1.62(3H,d), 2.9—3.5(4H,m), 4.45(1H,t), 5.25(1H,q), 6.40(1H,br), 6.6—7.5(9H,m)
9—(3)	N-methyl-N-butyl-2-chloro-3-[4-(1-phenyl)-ethyloxy)phenyl]propionamide oily substance NMR spectrum (δ ppm $CDCl_3$) 0.87(3H,t), 1.0—1.5(4H,m), 1.57(3H,d), 2.83(3H,s), 2.8—3.5(4H,m), 4.53(1H,t), 5.27(1H,q), 6.5—7.5(9H,m)

WHAT WE CLAIM IS:—

1. A compound of the formula (I):



(I)

wherein R^1 represents a hydrogen atom, a lower alkyl group having 1 to 5 carbon atoms, a halogen atom, hydroxyl group, a lower alkoxy group having 1 to 4 carbon atoms or a trifluoromethyl group; R^2 and R^3 are the same or different and each represents a hydrogen atom or a lower alkyl group having 1 to 5 carbon atoms; Y represents an alkylenethio group having 1 to 6 carbon atoms, an alkyleneoxy group having 1 to 6 carbon atoms or an alkylenedioxy group having 1 to 6 carbon atoms; Z represents a carboxyl group or a group convertible to a carboxyl group; and n is 1 or 2, or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein Y is an alkylenethio group having 1 to 6 carbon atoms.

3. A compound as claimed in claim 1, wherein Y is an alkyleneoxy group having 1 to 6 carbon atoms.

4. A compound as claimed in claim 1, wherein Y is an alkylenedioxy group having 1 to 6 carbon atoms.

5. A compound as claimed in any of claims 1 to 4 wherein R^2 is a hydrogen atom.

6. A compound as claimed in any of claims 1 to 4, wherein R^2 is an alkyl group having 1 to 5 carbon atoms.

7. A compound as claimed in any of claims 1 to 6, wherein R^3 is a hydrogen atom.

8. A compound as claimed in any of claims 1 to 6, wherein R^3 is an alkyl group having 1 to 5 carbon atoms.

9. A compound as claimed in any of claims 1 to 8, wherein R^1 is a hydrogen atom.

10. A compound as claimed in any of claims 1 to 8, wherein R^1 is a lower alkyl group having 1 to 5 carbon atoms.

11. A compound as claimed in any of claims 1 to 8, wherein R^1 is a halogen atom.

12. A compound as claimed in any of claims 1 to 8, wherein R^1 is an alkoxy group having 1 to 4 carbon atoms.

13. A compound as claimed in any of claims 1 to 12, wherein Z is a carboxyl group.

14. A compound as claimed in any of claims 1 to 12, wherein the group convertible to a carboxyl group, represented by Z, is a formyl group, cyano group, aminocarbonyl group, an alkoxycarbonyl group having 2 to 5 carbon atoms, a mono- or di-alkylamino-carbonyl group having 2 to 9 carbon atoms, a mono- or di-cycloalkylaminocarbonyl group having 6 to 13 carbon atoms, a mono or di-arylaminocarbonyl group having 7 to 16 carbon atoms, or a salt of the carboxyl group with a nontoxic cation or with an organic amine.

15. 2-Chloro-3-(4-benzyloxyphenyl)propionic acid.

16. 2-Chloro-3-(4-benzyloxyphenyl)propionamide.

17. Ethyl 2-chloro-3-(4-benzyloxyphenyl)propionate.

18. 2-Chloro-3-[4-(4-chlorobenzyloxy)propionic acid.

19. Ethyl 2-chloro-3-[4-(4-chlorobenzyloxy)phenyl]propionate.

20. 2-Chloro-3-[4-(3-chlorobenzyloxy)phenyl]propionic acid.

21. Ethyl 2-chloro-3-[4-(2-chlorobenzyloxy)phenyl]propionate.

22. Ethyl 2-chloro-3-[4-(4-fluorobenzyloxy)phenyl]propionate.

23. 2-Chloro-3-[4-(1-phenylethyloxy)phenyl]propionic acid.

24. Ethyl 2-chloro-3-[4-(1-phenylethyloxy)phenyl]propionate.

25. 2-Chloro-3-[4-(1-phenylpropyloxy)phenyl]propionic acid.

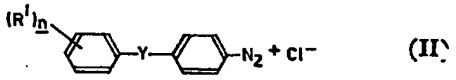
26. Ethyl 2-chloro-3-[4-(1-phenylpropyloxy)phenyl]propionate.

27. Ethyl 2-chloro-3-[4-(1-methyl-2-phenylethyloxy)phenyl]propionate.

28. Ethyl 2-chloro-3-[4-phenoxymethylphenyl)propionate.

29. Ethyl 2-chloro-3-[4-(1-phenoxyethyl)phenyl]propionate.

30. A method for producing a compound of the formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, which comprises reacting a compound of the formula (II):



(II)

wherein R^1, Y and n are as defined in claim 1,
with a compound of the general formula (III):

$$R^2CH=CR^3—Z \qquad \text{(III)}$$

wherein R^2, R^3 and Z have the same meanings as defined in claim 1.

31. A method as claimed in claim 30, wherein the reaction is conducted in the presence of a copper compound.

32. A method as claimed in claim 30, wherein the reaction is conducted in the presence of cuprous oxide, cupric oxide, cuprous chloride, cupric chloride, cuprous bromide, cupric bromide, copper nitrate or copper sulphate, alone or in admixture.

33. A compound as claimed in claim 1, substantially as herein described with reference to any of the specific Examples.

34. A method as claimed in claim 30, substantially as herein described with reference to any of the specific Examples.

35. A compound of formula (I) as defined in claim 1, when produced by a method as claimed in any of claims 30 to 32 and 34.

36. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 29, 33 and 35, together with a non-toxic pharmaceutically acceptable carrier or diluent therefor.

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